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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,794	10/23/2003	Jerome B. Zeldis	9516-076-999	2021

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,794	ZELDIS ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9,23 and 27-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9,23 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted December 7, 2007 wherein the rejections of record in the previous office action are traversed. This application claims benefit of provisional application 60/421003, filed October 24, 2002.

Claims 1-5, 9, 23, and 27-37 are pending in this application.

Claims 1-5, 9, 23, and 27-37 as amended are examined on the merits herein.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 7, 2007 has been entered.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 27-30, and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omogui et al. (US patent publication 2004/0038874, of record in previous action) in view of Muller et al. (US patent 6281230, cited in PTO-892).

Omoigui discloses a method for the treatment of persistent pain by administering a drug that antagonizes one or more mediators of inflammation. (p. 1, paragraph 0004) Drugs useful in this manner include TNF-α blockers, (p. 2, paragraphs 0007 and 0011) including thalidomide and analogues as a specific embodiment. (p. 3, paragraph 0023) Reflex Sympathetic Dystrophy, otherwise known as chronic regional pain syndrome, is listed as a disease treatable by this method. (pp. 9-10, paragraphs 0078-0082)

Omoigui does not disclose a method using the specific compounds of the claimed invention in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34.

Muller et al. discloses a range of isoindilyl-piperidines including the claimed structure, that decrease levels of TNF-α *in vivo*. (column 4 line 38 - column 5 line 11, wherein R_{1-3} = H, R_4 = NH_2, X = C=O, Y = CH_2, R_6 = H) These compounds can be used to inhibit the undesirable effects of TNF-α in an animal in need thereof, and can be administered concurrently with an additional active agent. (column 5 lines 23-45) Dosage forms are disclosed having from 1-100 mg of drug per dose. (column 8, lines 27-35) The compound of the claimed invention, 3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione, is disclosed as one embodiment of the active agents useful in this therapeutic method.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the therapeutic method of Omoigui using the compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Muller et al. discloses that the claimed compound is a TNF-α inhibitor and thus useful in the method of Muller. One of ordinary skill in the art would have also recognized that the compound of Muller is a thalidomide analog, based upon the fact that it shares a common isoindilyl-piperidine core structure with thalidomide. Therefore it would be seen to be useful as a thalidomide analog in the method of Omogui et al. One of ordinary skill in the art would have been motivated to administer the compound orally and in combination with other active agents because these limitations are taught by Muller et al. for this compound. One of ordinary skill in the art would have been motivated to administer a dosage of 5-50 mg because this dosage range overlaps substantially with the dosage range of 1-100 mg taught by Muller et al. One of ordinary skill in the art would have been motivated to administer the compound as a tablet or capsule because these dosage forms are similar to the pill and lozenge oral dosage forms taught by Muller et al. One of ordinary skill in the art would have been motivated to administer the compounds as a pharmaceutically acceptable salt, solvate, or stereoisomer because these pharmaceutically acceptable dosage forms are routine and well known in the art for compounds to be administered as pharmaceuticals. One of ordinary skill in the art would have reasonably expected success in using this specific

compound because Muller et al. already discloses that the compound can be used to treat other TNF-dependant disorders. One of ordinary skill in the art would have reasonably expected success in using the specific claimed dosage form and amounts because determining the exact details of the dosage form to be administered is well within the ordinary and routine level of skill in the art. With respect to the dosage ranges of claims 33-35, one of ordinary skill in the art would have been motivated to test various dosages in order to optimize the therapeutic regiment for the particular disease being treated. (e.g. complex regional pain syndrome) and the particular route of administration (e.g. oral vs. intravenous) This experimentation is merely routine and predictable.

Thus the invention taken as a whole is *prima facie* obvious.

The following grounds of rejection of record in the previous office action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 27-30, and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, reference of record in

previous office action) in view of Olmarker et al. (PCT international publication WO02080891, of record in previous office action)

Omoigui discloses a method for the treatment of persistent pain by administering a drug that antagonizes one or more mediators of inflammation. (p. 1, paragraph 0004) Drugs useful in this manner include TNF-α blockers, (p. 2, paragraphs 0007 and 0011) including thalidomide and analogues as a specific embodiment. (p. 3, paragraph 0023) Reflex Sympathetic Dystrophy, otherwise known as chronic regional pain syndrome, is listed as a disease treatable by this method. (pp. 9-10, paragraphs 0078-0082) Omoigui does not disclose a method using the specific compounds of the claimed invention in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34.

Olmarker et al. discloses a method of treating low back pain due to leakage of the nucleus pulposus from a damaged intervertebral disk, comprising administering a TNF inhibitor. (pp. 4-6) Because the mechanism of this pain involves the irritation of an affected nerve, it is considered to be a form of neuropathic pain. Specific compounds useful in the method of Olmarker et al. include thalidomide derivatives, including the compound CDC-501, which according to its chemical abstracts registry entry, is identical to the immunomodulatory compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione used in the claimed method. (p. 7, lines 24-26, see also chemical abstracts registry number 191732-72-6) The compound can be administered orally as a pill, syrup, or lozenge, (p. 9, lines 11-12) in an oral dose of 10-300 mg. (p. 9,

line 20) The compounds can be administered in combination with other active agents. (p. 12, lines 4-7)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the therapeutic method of Omoigui using the compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Olmarker et al. discloses that the claimed compound is a TNF-α inhibitor and a thalidomide analog, and thus useful in the method of Olmarker. One of ordinary skill in the art would have been motivated to administer the compound orally and in combination with other active agents because these limitations are taught by Olmarker for this compound. One of ordinary skill in the art would have been motivated to administer a dosage of 5-50 mg because this dosage range overlaps substantially with the dosage range of 10-300 mg taught by Olmarker et al. One of ordinary skill in the art would have been motivated to administer the compound as a tablet or capsule because these dosage forms are similar to the pill and lozenge oral dosage forms taught by Olmarker. One of ordinary skill in the art would have been motivated to administer the compounds as a pharmaceutically acceptable salt, solvate, or stereoisomer because these pharmaceutically acceptable dosage forms are routine and well known in the art for compounds to be administered as pharmaceuticals. One of ordinary skill in the art would have reasonably expected success in using this specific compound because Olmarker et al. already discloses that the compound can be used to treat other TNF-

dependant pain syndromes such as lower back pain. One of ordinary skill in the art would have reasonably expected success in using the specific claimed dosage form and amounts because determining the exact details of the dosage form to be administered is well within the ordinary and routine level of skill in the art. With respect to the new dosage ranges of claims 33-35, one of ordinary skill in the art would have been motivated to test various dosages in order to optimize the therapeutic regiment for the particular disease being treated. (e.g. CRPS vs. low back pain) and the particular route of administration (e.g. oral vs. intravenous) This experimentation is merely routine and predictable.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 9, 2007, have been fully considered as they relate to the above ground of rejection, but are not persuasive to remove the rejection. Applicant argues that Omoigui discloses thousands of compounds useful for treating pain and does not specifically cite a narrow range of particular thalidomide analogs. However, according to MPEP 2123, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Omogui teaches that various antiinflammatory agents can be used to treat certain kinds of pain, for example complex regional pain syndrome. The fact that Omogui discloses a broad range of inflammatory mediators does not discredit or teach away from the use of any one particular

inflammatory mediator, so long as that mediator belongs to a class of compounds that has been specifically recited by Omogui.

Applicant further argues that the compounds of Olmarker et al. do not possess sufficient structural similarity to thalidomide for one of ordinary skill in the art to expect similarity in biological function. However, the structural similarity is not cited to support a case of similar biological function according to *in re Grabiak*, but rather to merely establish that these compounds can be reasonably considered to be "thalidomide analogs". Unlike *Takeda* and *Grabiak*, the present case does not involve the unsupported assertion that two compounds will function similarly merely based on structural similarity, but rather that these compounds qualify as "thalidomide analogs" under the definition used by Omogui. Furthermore, Olmarker et al. already states that these compounds inhibit TNF-α, which would already indicate to someone of ordinary skill in the art that they possess the same biological activity as thalidomide when used in the method of Omogui. Applicant also cites *Takeda* to say that the cited prior art provides a broad selection of compounds any of which could have been selected as the lead compound" rather than a "finite number of identified, predictable solutions." However, in this case, Olmarker et al. does in fact cite a finite number of definite, well-defined species, such as for example the species CDC-501 described above, known as a TNF-α inhibitor, which is also a compound of the claimed invention.

Applicant also argues that one of ordinary skill in the art would not have hade a reasonable expectation of success in varying all parameters of each of numerous possible choices in order to arrive at the claimed invention. However, given that

Olmarker et al. already discloses the compound CDC-501, which is a specific compound with a well-defined chemical structure, as being a TNF-alpha blocker useful for treating pain, no extensive variation of multiple parameters would be necessary to practice this embodiment.

Still further, Applicant argues that the prior art teaches away from the claimed dosage range because Olmarker et al. discloses a broad dosage range for administering TNF-alpha inhibitors in general and a narrow preferred dosage range for administering CDC-501 that is higher than the dosage in instant claims 35-37. However, as discussed above, preferred embodiments are not considered to constitute a teaching away from the claimed invention if the prior art otherwise renders the claimed invention obvious. Furthermore, the ranges listed for administering CDC-501 are meant fir oral administration. Other methods of administration, such as those listed on p. 9 of Olmarker et al., for example intravenous administration or inhalation, would naturally require lower doses, such as those recited in the instant claims.

Finally, Applicant argues that the claimed invention produces unexpected results when compared to the prior art. However, the document relied upon to provide evidence of unexpected results is not seen to be enclosed with the current response or to be cited in any of the previously filed information disclosure statements. Furthermore, it is not part of the specification as originally filed or any subsequent affidavit or declaration. Therefore no evidence of unexpected results is seen to exist.

For these reasons the rejection is deemed proper and maintained.

Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, reference of record in previous office action) in view of Olmarker et al. (PCT international publication WO02080891, of record in previous office action) in view of Remington. (of record in previous office action)

The disclosure of Omoigui in view of Olmarker et al. is discussed above. Olmarker et al. does not disclose a method comprising administering the therapeutic compound in an enantiomerically pure form.

Remington discloses that different enantiomers of the same compound may possess different biological and pharmacological activities. (pp. 462-463)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Omoigui in view of Olmarker using enantiomerically pure 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. One of ordinary skill in the art would have been motivated to practice the invention in this manner because, as Remington discloses that the two enantiomers of a chiral compound possess different activities *in vivo*, it stands to reason that one of the two enantiomers of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione possesses better activity and/or reduced side effects compared to the other enantiomer, and is thus a better drug in its enantiomerically pure form. One of ordinary skill in the art would reasonably have expected success because testing two enantiomers for a known activity to determine which is the best drug candidate is a small and routine experimental burden well within the ordinary level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 9, 2007, have been fully considered as they relate to the above ground of rejection, but are not persuasive to remove the rejection. Applicant's arguments with respect to this rejection are the same as those made with respect to the above rejection over Omogui in view of Olmarker, and are not found persuasive for the same reasons. Therefore the rejection is deemed proper and maintained.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
3/3/2008

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623